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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,174	11/26/2003	Katrin Kneipp	M0925.70114US01	5755

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,174	KNEIPP ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *188-195 and 198-201* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. en closed
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-17,19, 23-37,39,43-58,60,64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135,138,139,146,147,153,155-157,159-162,164,172,179,180,182,183 and 187-198.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-17, 19, 23-37,39,43-58,60,64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135,138,139,146,147,153,155-157,159-162,164,172,179,180,182,183, 187 and 196-197.

DETAILED ACTION

Amendment Entry

1. The amendment filed March 6, 2006 has been entered. Claims 188-189, 195 and 198 have been amended. Claims 199-201 have been newly added. Claims 1-17, 19, 23-37,39,43-58,60,64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135,138,139,146,147,153,155-157,159-162,164,172,179,180,182,183, 187 and 196-197 have been withdrawn from consideration. Claims 18, 20-22, 38, 40-42, 59, 61-63, 73, 75-77, 86, 88-90, 118-121, 123-124, 127, 129, 131, 136-137, 140-145, 148-152, 154, 158, 163, 165-171, 173-178, 181, 184-186 have been cancelled. Claims 188-195, and 198-201 are under consideration in this office action.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 188-195 and 199-201 of this application. However, provisional application 60/076,310, fails to teach the instantly claimed method. There is no teaching of a method for determining a sequence of at least a portion of a DNA or RNA strand comprising the instantly recited steps. Thus, priority cannot be granted to 60/076,310, since what is now claimed, has not been previously recited in that application.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The written description rejection of claims 188-195 and 198 under 35 U.S.C. 112, first paragraph;

b) The new matter rejection of claims 188-195 and 198 under 35 U.S.C. 112, first paragraph;

c) The rejection of claims 188-190 and 198 under 35 U.S.C. 112, second paragraph; and

d) The rejection of claims 188-195 and 198 under 35 U.S.C. 102(b) as being anticipated by Graham et al., (WO 97/05280).

Response to Arguments

4. Applicant's arguments filed March 6, 2006 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. The rejection of claims 190-194 are drawn to the method wherein the nucleic acid comprises labeled thymine, adenine, cytosine, guanine or uracil. It is unclear when the nucleic acids became labeled. There is no step within the method to provide for the

nucleic acids to be labeled. It is also unclear how the nucleic acid and unidentified sequence will already comprise a labeled thymine, adenine, cytosine, guanine or uracil. Therefore, clarification is required to overcome the rejection.

Claims 190-194 recites the limitation "the nucleic acids" in the claims. There is insufficient antecedent basis for the limitation in the claims.

New Grounds of Rejection
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 188-195 and 198-201 are rejected under 35 U.S.C. 102(b) as being anticipated by Vo-Dinh (US Patent 5,306,403). The claims are drawn to a method for determining a sequence of at least a portion of a DNA or an RNA strands comprising: a) fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments each fragment comprising at least one base;
b) sequentially identifying each of the one or more fragments by Raman spectroscopy; and c) determining the sequence of at least a portion of the DNA or RNA strand based on the sequential identification of each of the one or more fragments. The dependent claims are drawn to using a labeled fragment or bases, using SERS or SERRS spectroscopy and using specific metal surfaces.

Vo-Dinh (US Patent 5,306,403) teaches raman-based SER(R)S analysis systems for DNA sequencing. The art teaches that for DNA sequence analysis, four different labels were used for the specific bases, adenine, cytosine, guanosine, and thymidine (col. 2, lines 27-36). Vo-Dinh teaches the attachment of a surface enhanced Raman scattering (SERS) label on the DNA fragments for sequencing (col. 4, lines 1-4). One embodiment teaches that the SERS labels were attached to the DNA fragments or oligonucleotides and after separation of the DNA fragments, the SERS labels can be detected when they are still bound to the DNA fragments (col. 6, lines 45-49). A variation of this technique would involve detecting the SERS labels after the SERS labels are selectively detached from the DNA fragments and transferred onto a SERS substrate surface (col. 6, lines 49-53). The sequencer apparatus allows for sequential identification by providing a running gel (col. 6, lines 56-59). In order to cleave DNA fragments, restriction enzymes, also known as endonucleases can be selected as SERS labels. The enzymes recognize specific base sequences and cleave the strands at specific places (col. 8, lines 64-68). In general, restriction enzymes recognize specific sequences and hydrolyzes a phoshodiester bond in the DNA strand, thereby allowing a SERS-active compound to be attached to a specific base pair sequence that can be selectively cleaved by the endonuclease (col. 9, lines 1-10). Thus, the patent teaches using a nuclease, i.e., the endonuclease, to form a plurality of fragments comprising at least one base, just as required by the claims. The label is a specific chemical group that can be detected using SERS spectrographic techniques (col. 4, lines 4-6). After separation of the DNA fragments, the SERS labels are detected by focusing a light

source onto a surface of a SERS-active coating (col. 4, lines 29-33). The coating can be made of alumina wherein the alumina metal covers the whole surface of glass (col. 4, lines 60-63). Furthermore, silver deposition can be performed (col. 4, lines 66-68). Also, SERS-active species may be metal sols or microparticles, such as ones well known in the art (col. 5, lines 23-25). Thus the surface to which the fragment is attached can be metal film or a particle, just as required by the claims.

Thus, Vo-Dinh teaches a method for determining a sequence of at least a portion of a DNA or an RNA strands comprising: a) fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments each fragment comprising at least one base, b) sequentially identifying each of the one or more fragments by Raman spectroscopy; and c) determining the sequence of at least a portion of the DNA or RNA strand based on the sequential identification of each of the one or more fragments just as required by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 188-195, 198-199 and 201 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorre et al., in view of Kneipp et al., (Physical Review Letters, Vol. 78(9):1667-1670 March, 1997).

The claims are drawn to a method for determining a sequence of at least a portion of a DNA or an RNA strands comprising: a) fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments each fragment comprising at least one base; b) sequentially identifying each of the one or more fragments by Raman spectroscopy; and c) determining the sequence of at least a portion of the DNA or RNA strand based on the sequential identification of each of the one or more fragments. The dependent claims are drawn to using a labeled fragment or bases, using SERS or SERRS spectroscopy and using specific metal surfaces.

Dorre et al., teach techniques for single molecule sequencing. The techniques allow for the identification of RNA or DNA, wherein a single molecule with fluorescent analogs can be fixed in a microstructure channel (page 140). The molecule may be degraded sequentially with the help of an exonuclease (page 140). This provides for the release on monomers which can be detected according to their liberation from the polymer substrate, thus sequence analysis can be performed at the rate of enzymatic degradation (page 140). Therefore, the art teaches fragmenting the bases using a nuclease, in the form of an exonuclease and sequential identification just as required by the claims. The detection occurs using fluorescence correlation spectroscopy (page 140). Therefore the art teaches techniques for single molecule sequencing just as required by the claims. However, Dorre et al., do not teach using Raman spectroscopy to identify and determine the sequence of the DNA or RNA.

Kneipp et al., (March, 1997) teach single molecule detection using surfaced-enhanced raman scattering (SERS). Kneipp et al., teach that methods for selective and

rapid detection of single molecules using excited fluorescence is already known in the art (page 1667). Raman spectroscopy is spectrochemical technique that is complementary to fluorescence but offers additional aspects: 1) SERS's vibrational spectrum provides a high degree of structural information about the molecule; 2) SERS allows for shorter integration times for detecting a molecules or higher rates for counting single molecule; and 3) SERS avoids photodecomposition of the probed molecules because the excitation energy is not in resonance with molecular transitions (page 1667). Furthermore, SERS is useful technique resulting in strongly increased Raman signal from molecules which have been attached to nanometer sized metallic structures (page 1667). The report uses colloidal silver solution at the single molecule level with no emission enhancing dyes (page 1667). See also Figure 2b. Therefore the art teaches using a metal particle surface and bases free of emission enhancing aids, just as required by the claims

Accordingly, it would have been prima facie obvious at the time of applicants invention to modify the method for determining a sequence of at least a portion of a DNA or an RNA as taught by Dorre et al., wherein the modification exchanges fluorescence detection for SERS detection as taught by Kneipp et al., because Kneipp et al., that raman spectroscopy is complementary to fluorescence but offers additional properties. One would have a reasonable expectation of success in determining the sequencing method using raman spectroscopy instead of fluorescence since it provides a high degree of structural information about the molecule; requires shorter time for detection and avoids photodecomposition. Furthermore, no more than routine skill

would have been required to exchange the detection methods when both methods are known to detect single molecules, and the art teaches that single molecule detection can identify DNA or RNA sequences using nuclease fragmentation and sequential identification and determination of the sequence.

Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Berlin et al., (US Patent 6,852,492) teach nucleic acid sequence by Raman monitoring. Su et al., (US Patent 6,912,173) teach nucleic acid sequencing wherein exonuclease treatment releases the labeled nucleotide for enhanced Raman spectroscopy detection.

Conclusion

9. No claims allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines

April 6, 2006

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